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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
COUNTS, GARY W	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 12/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,788	NGUYEN ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/12/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-99* is/are pending in the application.

4a) Of the above claim(s) *32-48 and 61-99* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-31 and 49-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The amendment filed October 12, 2005 is acknowledged and has been entered.

Election/Restrictions

1. Newly submitted claims 61-99 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Independent claims 61, 77, and 78 requires different cytokines and independent claims 1, 18 and 20 do not require these limitations.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 61-99 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Currently claims 1, and 4-99 are pending. Claims 32-48 and 61-99 are withdrawn from further consideration.

Remarks

It is noted that Applicant has amended the claims to include subject matter previously recited in claims 2 & 3. However, upon further consideration of the limitations of claims 2 & 3 the following rejections have been made. Examiner apologizes for any inconvenience caused to the Applicant.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 4- 6, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (US 6,767,708) in view of Boguslaski et al (US Patent 5,420,016).

Williams et al disclose the removal of multiple steroids (target analytes) from a biological sample (col 2, col 4, col 6). Williams et al disclose that this biological fluid which has been stripped of the steroids (target analytes) is used to generate calibrators and or controls. Williams et al disclose spiking the stripped serum with known concentrations of the target analytes.

Williams et al differ from the instant invention in failing to disclose packaging the components into a kit.

Boguslaski et al disclose assembling various system components into a test kit. By assembling these components into test kits, it makes it more convenient and facile for the test operator (col 7, lines 8-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to assemble the various reagents and components such as taught by Williams et al into kits because Boguslaski et al shows packaging these reagents and components into kits make it more convenient and facile for the test operator.

With respect to the limitations "in which the standard diluent is produced by removing the two or more different target analytes from the biological fluid by affinity chromatography or is obtained from a biological fluid of a host having the biological fluid substantially free of the two or more different target analytes" has not been given patentable weight because the limitations are directed to a product and not a method. The limitations read as a requirement to an assay. Further, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production and if the product in a product by process claim is

the same or obvious from a product in the prior art then the claim is unpatentable. Thus the combination of Williams et al and Boguslaski et al read on the instantly recited claims. See also the limitations of claim 4.

6. Claims 1, 4-8, 11, 12, 15-17 and 49-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al. (US 5,587,294) in view of Barrera et al. (Lymphokine and Cytokine Research, Vol 11, No. 2, 1992, pp. 99-104) or Williams et al (US 6,767,708).

Tamarkin et al disclose a kit comprising a standard diluent and standards (control) to serve as assay standard (col 13). Tamarkin et al disclose that the diluent can be a serum solution (biological fluid) from which endogenous IL-1 or IL2 (target analytes) have been removed (col 16 –col 17). Tamarkin et al disclose known amounts of cytokines are added to the diluent to generate standard curves (col 17, lines 10-44). Tamarkin et al disclose that the kit can contain instructions (col 13, lines 13-16). Tamarkin et al also disclose that the kit comprises a solid phase carrier (support) (col 13). Tamarkin et al disclose that the carrier has immobilized antibodies to capture the target analyte (col 10, lines 44-63) (col 14, lines 21-25). Tamarkin et al also disclose that the solid support can be a bead (microparticles) (col 10, line 64 – col 11, line 6). Tamarkin et al disclose the kit can comprise labeled antibodies for the target analyte (col 14).

Tamarkin et al differ from the instant invention in failing to that the standard diluent is substantially free of two or more different target analytes.

Barrera et al disclose the depletion of cytokines from a biological fluid to be used as diluent in cytokine assays. Barrea et al disclose the removal of two different cytokines from the biological fluid (p. 99). Barrera et al disclose that the removal of these cytokines (target analytes) from the biological fluid provides for a matrix similar to the sample and this avoids loss of paralleism and improves sensitivity.

Williams et al disclose the removal of multiple analytes from a biological sample (col 2, col 4, col 6). Williams et al disclose this provides for a diluent which displays a behavior in the assay similar to that of the bodily fluid which is to be assayed for the analyte (col 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a diluent that has been depleted of two analytes such as taught by Barrera in the kit of Tamarkin et al because Barrera et al teaches the removal of these cytokines (target analytes) from the biological fluid provides for a matrix similar to the sample and this avoids loss of paralleism and improves sensitivity and that cytokine-free plasma should preferably be used as diluent. Further, this would provide for a single diluent as opposed to two separate diluents and therefore would be more convenient for the test operator.

It would have also been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a diluent that has been depleted of multiple analytes such as taught by Williams et al in the kit of Tamarkin et al because Williams et al teaches the removal of multiple analytes from a biological sample provides for a diluent which displays a behavior in the assay similar to that of the bodily fluid which is to be

assayed for the analyte. Further, as one of ordinary skill would recognize, this would provide for a single diluent in the kit as opposed to two separate diluents and therefore would be more convenient for the test operator.

With respect to the limitations "in which the standard diluent is produced by removing the two or more different target analytes from the biological fluid by affinity chromatography or is obtained from a biological fluid of a host having the biological fluid substantially free of the two or more different target analytes" has not been given patentable weight because the limitations are directed to a product and not a method. The limitations read as a requirement to an assay. Further, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production and if the product in a product by process claim is the same or obvious from a product in the prior art then the claim is unpatentable. Thus, the teachings of Tamarkin and Barrera reads on the instantly recited claims.

With respect to claims 50-53 as instantly recited. The number of different target analytes as recited in the instant claims. The removal of more than two different target analytes is viewed as an optimization of the prior art modified method and kit of Tamarkin et al and Barrera et al wherein two different target analytes are removed from a biological fluid to form a diluent. Absent evidence to the contrary the removal of more than two target analytes and the addition of the more than to analytes to the standard control would merely require adjustment in order to substantially free the biological fluid of the target analytes. Therefore, it would have been obvious to one of ordinary skill in the art to remove more than two different target analytes, since it has long been held

that the provision of adjustability, here needed, involves only routine skill in the art. *In re Stevens,* 101, USPQ 284 (CCPA 1954).

7. Claims 10, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al and Barrera et al or Williams et al in view of Posner et al (US 4,994,375).

See above for teachings of Tamarkin et al, Barrera et al and Williams et al.

Tamarkin et al, Barrera et al and Williams et al differ from the instant invention in failing to teach the two or more different target analytes are mixed together to form a single concentrated material.

Posner et al disclose combining different analytes to prepare controls or calibrants (col 2, lines 45-49) (col 3, lines 15-55). Posner et al disclose that the analyte are mixed and lyophilized and stored for later use (col 3, lines 15-68). Posner et al teaches that this control or calibrant is reconstituted by diluent (col 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the target analytes as taught by Tamarkin et al to form a single concentrated material because Posner et al teaches the combination of different analytes to prepare controls or calibrants which are lyophilized and stored for later use. Further, one of ordinary skill would recognize that the combination of analytes to form a single concentrated material provides for a single control that can replace two or more separate control products.

8. Claims 9, 13, 14, 20-23, 25-31 and 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al and Barrera et al or Williams et al in view of Oliver et al.

See above for the teachings of Tamarkin et al and Barrera et al and Williams et al.

Tamarkin et al, Barrera et al and Williams et al differ from the instant invention in failing to teach the solid supports are classifiable into subgroups, each subgroup differentiable from others by a differentiation parameter and each subgroup having immobilized thereon a capture reagent capable of binding to a different target analyte.

Oliver et al disclose polystyrene microparticles (solid supports) that are differentially stained and produces an array of 64 individually addressable populations of microspheres (p. 2058). Oliver et al disclose the microspheres comprise immobilized capture reagents such as antibodies for the specific cytokines (p. 2058). Oliver et al disclose calibrators and diluents for the calibrators (p. 2058 & 2059). Oliver et al disclose the diluent can comprise serum. Oliver et al disclose fluoresceinated detection reagents. Oliver et al disclose that the anlaytes can be GM-CSF, IL-2, IL-4 and TNF-a. Oliver et al discloses that these microspheres provide for the simultaneous quantitation of cytokines and decreases assay time from several hours to less than or equal to an hour and also decreases the total amount of sample required and reduces the potential for error because sample splitting is not required (p. 2058).

It would have been obvious to one of ordinary skill in the art at the time the inventions was made to incorporate microspheres as taught by Oliver et al into the

modified method and kit of Tamarkin et al because Oliver et al shows that these microspheres provide for the simultaneous quantitation of cytokines and decreases assay time from several hours to less than or equal to an hour and also decreases the total amount of sample required and reduces the potential for error because sample splitting is not required.

With respect to claim 24 the limitation is not given patentable weight (see 103 rejection of claim 1).

9. Claims 20-23, 27-31, and 55-57 rejected under 35 U.S.C. 103(a) as being unpatentable over Oliver et al (Multiplexed Analysis of Human Cytokines by use of the FlowMetrix System, Clinical Chemistry 44, No. 9, 1998) in view of Boguslaski et al (US Patent 5,420,016).

Oliver et al disclose polystyrene microparticles (solid supports) that are differentially stained and produces an array of 64 individually addressable populations of microspheres (p. 2058). Oliver et al disclose the microspheres comprise immobilized capture reagents such as antibodies for the specific cytokines (p. 2058). Oliver et al disclose calibrators and diluents for the calibrators (p. 2058 & 2059). Oliver et al disclose the diluent can comprise serum. Oliver et al disclose fluoresceinated detection reagents. Oliver et al disclose that the anlaytes can be GM-CSF, IL-2, IL-4 and TNF-a.

Oliver et al differ from the instant invention in failing to disclose packaging the components into a kit.

Boguslaski et al disclose assembling various system components into a test kit. By assembling these components into test kits, it makes it more convenient and facile for the test operator (col 7, lines 8-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to assemble the various reagents and components such as taught by Oliver et al into kits because Boguslaski et al shows packaging these reagents and components into kits make it more convenient and facile for the test operator.

With respect to the limitations "in which the standard diluent is produced by removing the two or more different target analytes from the biological fluid by affinity chromatography or is obtained from a biological fluid of a host having the biological fluid substantially free of the two or more different target analytes" has not been given patentable weight because the limitations are directed to a product and not a method. The limitations read as a requirement to an assay. Further, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production and if the product in a product by process claim is the same or obvious from a product in the prior art then the claim is unpatentable.

With respect to claim 20 Oliver teaches on page 2058 that the saline diluent used with the calibrators contains bovine serum albumin. Therefore, Oliver is teaching a standard diluent. One of ordinary skill in the art would recognize that a saline diluent would not contain the target analytes. Also, the claims recite comprising language and since Oliver teaches the diluent would contain bovine serum albumin. Oliver is teaching

a diluent that comprises serum that would not contain the target analytes. Thus, the combination of Oliver and Boguslaski et al reads on the instantly recited claims.

10. Claim 54 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al and Barrera et al or Williams et al in view in view of Vignali (Multiplexed particle-based flow cytometric assays, Journal of Immunological Methods 243, September 2000, pgs. 243-255.

See above for teachings of Tamarkin et al, Barrera et al and Williams et al.

Tamarkin et al Barrera et al and Williams et al differ from the instant invention in failing to teach eight target analytes are cytokines.

Vignali discloses the detection of IL-6, IL8, IL10 and IFN-y by multiplexed particle-based flow cytometric assays using reagents for the specific analytes (pages 249-250).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate reagents such as taught by Vignali in the modified method and kit of Tamarkin et al because Vignali et al disclose that this provides for the simultaneous detection of multiple cytokines which provides the advantage of substantial savings in the cost of reagents and time required to perform the assay. Therefore one of ordinary skill in the art would have a reasonable expectation of success incorporating reagents such as taught by Vignali into the modified method and kit of Tamarkin et al.

11. Claims 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oliver et al and Boguslaski et al in view of Vignali (Multiplexed particle-based flow

cytometric assays, Journal of Immunological Methods 243, September 2000, pgs. 243-255.

See above for teachings of Oliver et al and Boguslaski et al.

Oliver et al and Boguslaski et al differ from the instant invention in failing to teach eight target analytes are cytokines.

Vignali discloses the detection of IL-6, IL8, IL10 and IFN-y by multiplexed particle-based flow cytometric assays using reagents for the specific analytes (pages 249-250).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate reagents such as taught by Vignali in the modified method and kit of Oliver et al because Oliver et al specifically teaches that the addition of new or additional cytokines to the panel only requires the addition of new microsphere sets. Therefore one of ordinary skill in the art would have a reasonable expectation of success incorporating reagents such as taught by Vignali into the modified method and kit of Oliver et al.

Response to Arguments

12. Applicant's arguments filed 10/12/05 have been fully considered but they are not persuasive.

Regarding Williams et al. in view of Boguslaski et al Applicant states that claims 2 and 3 are now incorporated into claim 1 and that claims 2 and 3 were not included in this rejection, so that their inclusion into claim 1 should make claim 1 and those dependent on it patentable over the Williams et al and Boguslaski et al combination.

Applicant argues that Williams et al. disclose only a process in which a standard diluent is prepared that has had all steroid removed in order to prevent interference with a steroid, and thus is not relevant to the present claims. This is not found persuasive because as stated above the limitations "in which the standard diluent is produced by removing the two or more different target analytes from the biological fluid by affinity chromatography or is obtained from a biological fluid of a host having the biological fluid substantially free of the two or more different target analytes" has not been given patentable weight because the limitations are directed to a product and not a method. The limitations read as a requirement to an assay. Further, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production and if the product in a product by process claim is the same or obvious from a product in the prior art then the claim is unpatentable. Thus the combination of Williams et al and Boguslaski et al read on the instantly recited claims.

Applicant argues that Barrera et al prepares a standard diluent that is missing only a single analyte- not a plurality of analytes. Applicant directs Examiner's attention to page 100, right hand column "The blood compartment contained ^{125}I-labled recombinant human IL-1B or TNF, while the plasma in the dialysate compartment did not contain radiolabled cytokine." Applicant argues that all of the experimental work in the Barrera et al reference describes the use of dialysis to remove a single cytokine from a blood sample and compare the resulting specimen with the original. No removal of two or more cytokines or production of a sample lacking two or more cytokines as

carried out. This is not found persuasive because Barrera et al specifically teaches on p. 99 left hand column that "the selection of an appropriate diluent for the standards is essential. To avoid loss of parallelism and to improve sensitivity, the diluent should possess a matrix similar to the sample. In the assay of circulating cytokines as interleukin-1B and tumor necrosis factor (TNF), cytokine-free plasma should preferably be used as diluent. As normal pooled plasma usually contains variable amounts of these cytokines, its purification before use as diluent for the standards in indicated." Further, it is well settled that a reference must be evaluated for all disclosures not just its preferred embodiments. *In re Mills,* 470 F. 2d649, 176 USPQ 196 (CCPA 1972). Applicant further argues that Examiner points to the term cytokines as evidence that the standard diluent contains more than one target analyte. Applicant states that despite the use of the plural term "cytokines", this reference discloses only a standard diluent lacking a single cytokine; the language relied on by the examiner refers to cytokines in general, not to a process involving a plurality of cytokines. This is not found persuasive because as stated above Barrera et al specifically teaches that interleukin-1B and (emphasis added) tumor necrosis factor (TNF), cytokine-free plasma should preferably be used as diluent. Therefore, Barrera et al teaches removing plural target analytes.

Applicant argues that the tertiary references do not make up for the deficiencies of Tamarkin et al and Barrera et al. This is not found persuasive because it is the Examiner's position that the combination of Tamarkin et al and Barrera et al teach removing plural target analytes and thus read on the instantly recited claims. Thus, the

combination of the tertiary references with Tamarkin et al and Barrera et al is maintained.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary Counts
Examiner
Art Unit 1641
November 28, 2005

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12/02/05